PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mitsuru MAEDA et al.

Confirmation No.: 8952

Application No.: 10/500,334

Group Art Unit: 1623

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Examiner: Traviss C. McIntosh, III

Title: 2-O-(β-D-GLUCOPYRANOSYL) ASCORBIC ACID, PROCESS FOR ITS PRODUCTION, AND FOODS AND COSMETICS CONTAINING COMPOSITIONS COMPRISING IT

DECLARATION BY HARUKAZU FUKAMI PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Harukazu Fukami, Ph.D., a citizen of Japan, declare as follows:

1. I reside at 36, Shimadezaike-cho, Kissyoin, Minami-ku Kyoto-shi, Kyoto, 601-8373, Japan.

2. I have been employed at Suntory Ltd.since Jan. 1985. My current title is Proffesor.

3. I have a doctoral degree in Mar. 1978 from Kyoto University. My Curriculum Vitae is attached hereto.

4. I am a named inventor on the above-identified patent application.

5. I have reviewed the most recent Office Action of the above-identified patent application. I have also reviewed Japanese Patent Application No. 53-098954 ["JP 53-098954"]. Based on my review, it is my understanding the U.S. Patent and Trademark Office has concluded that JP 53-098954 allegedly discloses the compound, 2-O-(β-D-glucopyranosyl)-L-ascorbic acid. 2-O-(β-D-glucopyranosyl)-L-ascorbic acid is claimed in the instant application.

6. Although JP 53-098954 recites 2-O-(β-D-glucopyranosyl)-L-ascorbic acid along with other ascorbic acid derivatives, the reference does not teach or suggest a means of synthesizing 2-O-(β-D-glucopyranosyl)-L-ascorbic acid.

7. I have conducted the following experiment. This experiment is analogous to the method described in JP 53-098954 on page 408 in Japanese. The method performed fails to synthesize 2-O-(β-D-glucopyranosyl)-L-ascorbic acid.

MATERIALS AND METHODS

8. A solution was prepared by dissolving 5,6-O-isopropylidene-L-ascorbic acid (2 g, 9.3 mmole) in DMSO (20 mL). Pottasium carbonate (1.28 g, 9.3 mmole) and benzyl bromide (1.1 mL, 9.3 mmole) were added to the solution and the resulting solution was heated at 50°C for 4 hours to synthesize a benzyl ether of L-ascorbic acid. At the end of the reaction, water (100 mL) was added to the reaction mixture followed by 1 N HCl (ca. 20 mL) to acidify the mixture. The acidified mixture was extracted with ethyl acetate (100 mL), then washed with water (50 mL) and saturated brine (50 mL, 2 times). The extract was evaporated to dryness under reduced pressure. The dry material was dissolved in 2 mL of dichloromethane. To determine the composition of the dry material, an aliquot of the organic solution was loaded on a silica gel TLC plate (Silica gel 60 F254, Merck), and the chromatograph was developed with Ethyl acetate/n-Hexane (1:2) as the solvent.

9. Based on the TLC analysis, the compounds present in the above reaction mixture were isolated through a silica gel column chromatography (40g, COSMOSIL 75SL-II-PREP, spherical, Nakalai Tesque, inc.) using ethyl acetate/n-hexane (3:7) as the solvent. The isolated compounds were subsequently identified by NMR analysis.

RESULTS

10. The TLC analysis indicated two major spots on the plate: Spot A (faster-migrating one) and Spot B (Fig. 1 - attached). The column chromatography likewise isolated Product A (220 mg) and Product B (1.1 g), corresponding to Spot A and Spot B respectively. NMR analysis identified Product A as 5,6-O-isopropylidene-2,3-di-O-benzyl-L-ascorbate (2,3-O-substituted compound) and Product B as 5,6-O-isopropylidene-3-O-benzyl-L-ascorbate (3-O-substituted compound) (Fig. 2- attached).

ANALYSIS AND CONCLUSION

11. Using the method described in ¶¶ 8-9, I conclude that the reaction did not produce 5,6-O-isopropylidene-2-O-benzyl-L-ascorbate (*i.e.*, the 2-O-substituted compound). I make this conclusion based on two facts. First, if the 2-O-substituted product were in fact produced, it would have migrated slower than Spot A on the TLC plate, because the 2-O-substituted compound is expected to have an R_f value less than that of the dibenzyl compound. However, Spot B is the only spot that moves slower than Spot A. Second, the NMR analysis of Spot B indicates that there is no detectable amount of the 2-O-substituted product. NMR analysis indicates that spot B is in fact 5,6-O-isopropylidene-3-O-benzyl-L-ascorbate (*i.e.*, a 3-benzyl compound) not a 2-benzyl compound.

12. Based on the above TLC and NMR analyses, the reaction disclosed in JP 53-098954 only produced 3-O- and 2,3-O-substituted compounds. The method fails to produce any detectable amount of a 2-O-substituted compound. Accordingly, the alleged teaching in JP 53-098954 fails to describe an enabled method to synthesize any 2-O-(β-D-glucopyranosyl)-L-ascorbic acid intermediate as well as the compound itself.

13. Therefore, it is my conclusion that that P 53-098954 did not provide sufficient guidance at the time in order to synthesize 2-O-(β-D-glucopyranosyl)-L-ascorbic acid. Therefore, while the name of the compound is given, no means of making it or its precursor is taught.

14. While this is not the experiment described in JP 53-098954, the results would be the same as those of the experiment discussed above, because the hydroxyl group at the 3-position is more acidic and reactive than the hydroxyl one of the 2-position, as would be known to a chemist.

15. I conclude that the reference lacks a disclosure that would have enabled the skilled chemist at the time to synthesize 2-O-(β-D-glucopyranosyl)-L-ascorbic acid.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2008 5 9. Harukazu Fukami

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